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Effect of korean red ginseng on colon anastomotic healing: A randomised controlled experimental study

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Abstract
Aim: Although vegetable medicinal products are used worldwide, their beneficial and harmful effects have not been well documented. The aim of this study was to assess the effect of Korean red ginseng (KRG) on the healing of experimental colonic anastomosis in a rat model.
Material and Methods: Forty rats were randomized into four groups as follows: control groups (A and B) and KRG groups (C and D). Surgical procedure consisted of a transection and handsewn anastomosis of the ascending colon. Animals daily received either KRG (50ml/kg) or an equal volume of water by gavages 5 days before operation and then the surgery was done. Rats in Groups A and C were sacrificed on postoperative day (POD) 3, rats in Groups B and D were sacrificed on POD 7. Anastomotic complications and anastomotic bursting pressure measurements were recorded. Following these measurements, the anastomotic segment was resected for hydroxyproline (HPO) and histopathological evaluation.
Results: No significant differences were found in anastomotic complications. The colonic bursting pressures in the KRG groups were statistically significantly better than in the control groups. The hydroxyproline content was also significantly higher in Group C than in Group A. Histological examination confirmed that KRG treatment significantly increased neovascularization, fibroblastic activity and collagen content compared with controls on POD 7.
Discussion: Peri-operative administration of the KRG has a positive influence on the healing of colonic anastomosis in rats.

Keywords
Korean Red Ginseng, Colon, Anastomosis

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Introduction

Colonic leaks occur as a consequence of defective anastomotic healing and are regarded as a troublesome issue in colorectal surgery. Defective colonic anastomotic healing results from many factors, including tension on the anastomosis line, ischemia, distal obstruction, infection, surgical technique, malnutrition, various medications, and disordered collagen metabolism [1]. Diverse causes of defective colonic anastomotic healing make surgery even more complicated [2,3]. In the study by Neumann et al. [4], despite recent advances in surgical techniques and technologic devices, the anastomosis leakage rate was reported to be 37% in colorectal cancer patients. A healthy colonic anastomosis requires ample tissue perfusion and adequate oxygen content [5].

Red Ginseng root (Panax ginseng Meyer) has found clinical use in China, Korea and Japan to treat a variety of disorders, including atherosclerosis, hepatic disorders, cerebrovascular disorders, hypertension, and post-menopausal disorder [6]. Red Ginseng root extracts in the form of topical ointment have also been administered for clinical purposes to treat atopic suppurative dermatitis, open wounds, and inflammatory skin conditions. Triterpene glycosides known as ginsenosides are the main active compounds found in ginseng, which have been scrutinized for their pharmacological properties. According to previous reports, ginsenoside Rg1 induces functional neovascularization into a polymer scaffold in vitro and angiogenesis in vivo [7]. In contrast, ginsenoside Rb1 and Rb2 inhibit angiogenesis, while the latter favors the proliferation of epidermal cells and improves wound healing [8,9]. According to a report by Morisaki et al. [10], Korean Red Ginseng (KRG) induced angiogenesis both in vitro and in vivo, in endothelial cell culture and in an animal model. Nevertheless, it has been understudied how and to what degree would KRG's angiogenic action affect colonic anastomosis. In this study, we investigated the effects of KRG on colonic anastomosis in rats.

Material and Methods

The experimental protocols were conducted with the approval of the Animal Research Committee at Bülent Ecevit University, Zonguldak. All animals were maintained in accordance with the recommendations of the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Ethical approval was received for this study from the ethics committee of Bülent Ecevit University, Zonguldak. Statistical analysis was performed with the SPSS version 13.0 ® software package (IBM, New York, USA).

Animals and Experiments

Forty female Wistar rats weighing 200 to 250 g were housed individually in cages, were allowed free access to standard rat chow and water before and after the experiments. The animal rooms were windowless with temperature (22±2°C) and lighting controls. The rats daily received either KRG (Sunsam Co Ltd, Namwon-Si Jeollabukdo, Korea) (50ml/kg) or an equal volume of water via gavages 5 days before the operation and then surgery. The animals were fasted overnight preoperatively but were given free access to water. The rats were divided into four groups after the operation (n = 10): postoperative day (POD) 3 untreated control group (Group A), POD 7 untreated control group (Group B), POD 3 KRG group (Group C) and POD 7 KRG group (Group D).

Surgical Procedure

Mechanical and antibacterial bowel preparation was not performed. After 12 h fasting, all rats were anesthetized with 5 mg/kg xylazine (Rhompun, Abdi Ibrahim, Istanbul, Turkey) and 40 mg/kg ketamine hydrochloride (Ketalar, Eczacıbasi, Istanbul, Turkey). To prevent postoperative dehydration, 5 ml of Ringer's lactate solution was injected subcutaneously. Through a midline incision, the right colon was transected and an end-to-end anastomosis was created using a single layer of 6 interrupted 6–0 polypropylene sutures (6–0 monofilament polypropylene; Prolene, Dogsan, Besiktas, Istanbul, Turkey). The abdominal muscle layers and skin incision were closed separately with running sutures (3–0 silk, Dogsan, Besiktas, Istanbul, Turkey). All anastomoses were done by the same surgeon, who was experienced in the techniques. The rats were anesthetized using the same method on POD 3 and POD 7. A repeat laparotomy was made through the same midline incision and the peritoneal cavity was opened. Anastomotic bursting pressure was measured as described below. The anastomotic segment was isolated from the surrounding tissue, and a part of it was collected for hydroxyproline assay as a marker of collagen content, and another part was collected for histopathologic examination. The animals were then sacrificed with an excess dose of ether.

Measurement of Bursting

Pressure. The anastomosis line was found and the intestine was cut out 2 cm proximally and 2 cm distally to the anastomosis region using the same method used by Li et al. [11]. One end was sutured and the other end was tied after an 18 g intraluminal catheter placement. A three-way cannula was placed on the tip of the catheter. One end was connected to intraluminal side and the other end was connected to the manometer. Methylene blue, diluted with saline, was administered at 6 ml/min speed with an infusion pump. The pressure when the blue colored fluid was seen, or the time when a sudden drop in pressure was seen, was defined as the burst pressure and was recorded in mm Hg.

Measurement of Hydroxyproline Level

Tissue samples were homogenized and stored at -40°C. An autoclave was used to hydrolyze the specimens. Chloramine-T was added to provide oxidation at room temperature. Finally, Ehrlich reactive was also used to stain samples measured at 550 nm using a spectrophotometer [12]. Hydroxyproline levels were calculated as µg/g wet tissue weight from the calibration curve. These assessments were provided by a biochemist blinded to the study.

Histopathological Examinations

Histopathological examinations were conducted by the same pathologist. The sample pieces were prepared in a paraffin block after which their thin cross-sections were dyed using "hematoxylin-eosin" (H-E) dye and examined under a light microscope. The images were recorded on a computer. Histopathological staging of the anastomotic line was conducted according to the Ehrlich-Hunt Model [13]. Evaluation criteria in this model are the number of inflammatory cells,

fibroblasts, neovascularization, and collagen.

Statistical Analysis

Statistical analysis was performed with the SPSS version 13.0 software package (IBM, New York, USA). Continuous variables were given with mean, median, standard deviation, minimum and maximum values. Normality analyses were performed using the Shapiro-Wilk test in order to evaluate the distribution of the data. Then, dual and triple comparisons among groups were performed using the Mann-Whitney U and Kruskal-Wallis Tests, respectively. P-values less than 0.05 were considered statistically significant.

Results

No anastomotic complications (dehiscence of the anastomosis or death) occurred in the animals, and a gross observation of circumferential healing of anastomotic lines was documented. Anastomotic wound healing was evaluated by means of bursting pressure, hydroxyproline content and histopathological assessment.

Bursting Pressure and Hydroxyproline Content

In all subjects, the bursting was observed at the anastomotic line, mean anastomotic bursting pressures were 43.00±10.27 mmHg in Group A, 70.40±8.39 mmHg in Group B, 84.60±13.10 mmHg in Group C and 159.00±19.07 mmHg in Group D (Table 1). Mean bursting pressure was higher in the subjects who were treated with KRG than in those who were not treated with KRG. Significant statistical differences have been detected among Groups A and C, and Groups B and D (p=0.003 and p<0.001 respectively).

According to hydroxyproline levels (mcg/tissue) of the subjects, mean values of the groups were detected as 174.4 ± 14.85 for Group A, 195.64 ± 9.52 for Group B, 184.62 ± 7.65 for Group C, and 190,86 ± 16.04 for Group D (Table 1). There was significantly greater anastomotic hydroxyproline content in Group C than in Group A (p=0.012). Mean values in Groups B and D were nearly similar, and Group B had higher hydroxyproline concentrations compared with Group D.

Histopathological Results

According to histopathological staging results based on the Ehrlich-Hunt model, the average values of the groups were detected as 5.20 ±1.13 for Group A, 8.30±2.49 for Group B, 6.00±1.88 for Group C, and 11.60±2.22 for Group D (Table 1). To evaluate wound healing in the anastomotic line, according to the histopathological staging based on the Ehrlich-Hunt model, fibroblastic activity, neovascularization, and collagen measured in Group A and Group C in the POD 3 are in low degrees, and the difference was insignificant. However, inflammatory cell infiltration was higher in Group A compared to Group C, but was not find statistically significant (Table 1). There were significant differences in fibroblastic activity, collagen, and neovascularization between the POD 7 groups (p<0.001, <0.001 and p=0.002 respectively), whereas there was no significant

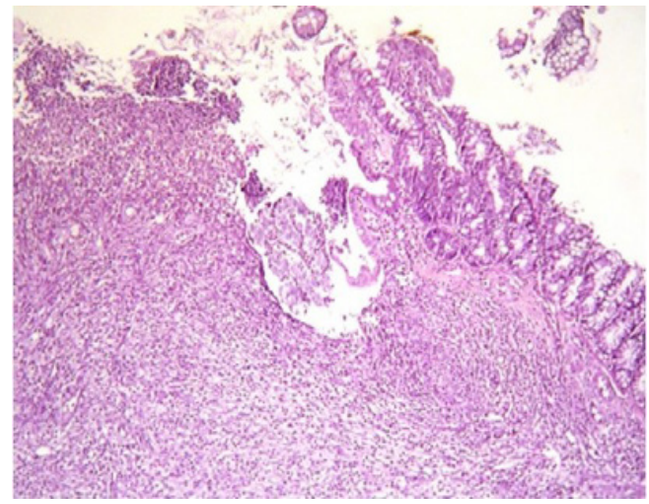

Figure 1. Minimal fibroblastic activity, collagen deposition and vessel proliferation in Group C (H&E:10x)

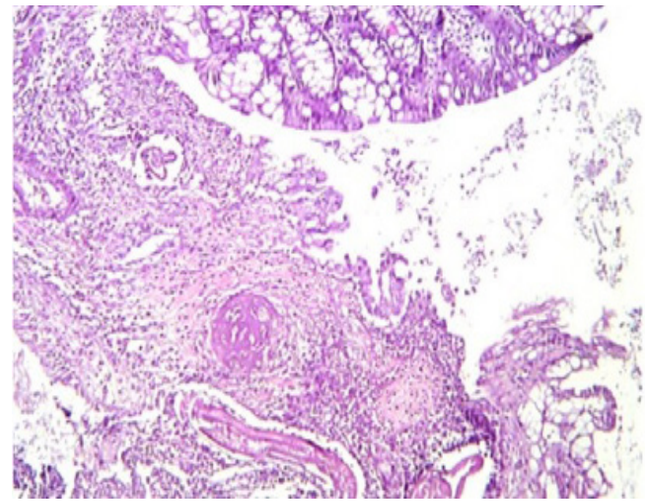

Figure 2. Intense fibroblastic activity, collagen deposition and vessel proliferation in Group D (H&E:10x)

Table 1. Comparison of bursting pressure and hydroxyproline levels and histopathological variables and scores within the groups

	POD 3		p	POD 7		p
	Group A	Group C		Group B	Group D	
Bursting pressure (mmHg)	43.00±10.27	84.60±13.10	0.003	70.40±8.39	159.00±19.07	<0.001
Hydroxyproline level (mcg/gram tissue)	174.4 ± 14.85	184.62 ± 7.65	0.012	195.64 ± 9.52	190,86 ± 16.04	0.644
Histopathological variables and score						
Total score	5.20±1.13	6.00±1.88	0.824	8.30±2.49	11.60±2.22	0.004
Inflammatory cell	1.90±0.56	1.30±0.48	0.311	2.40±1.07	2.00±0.47	0.311
Fibroblastic activity	1.00±0.00	1.50±0.52	0,071	2.00±0.47	3.50±0.52	<0.001
Neovascularization	1.20±0.42	1.40±0.51	0.862	2.10±0.56	3.10±0.73	0.002
Collagen	1.10±0.31	2.00±0.66	0.252	1.80±0.63	3.20±0.91	<0.001

POD: Postoperative day

difference in inflammatory cell infiltration between Group B and Group D (Table 1). Sample microscopic images of the histopathological examination are shown in Figures 1 and 2.

Discussion

A large variety of local or systemic factors affect anastomotic healing, of which tissue perfusion and oxygenation are the two major determinants [5,14]. Colonic anastomoses suffer from a greater rate of leaks compared to other parts of the gastrointestinal system due to some of their unique biological differences, including low collagen content, high collagenase activity, poor collateral circulation, and the lack of a serosa in the extra peritoneal rectum. Studies on colonic anastomosis have focused on certain substances that have proven effective in improving the pathophysiological healing process. Various modes of action to achieve that goal include hastening wound healing, promoting vascularization, and eliminating septic factors. Local tissue perfusion at the site of anastomosis is usually regarded as the most important factor for proper healing [15]. Body sites where tissue repair or regeneration takes place are in an increased need for nutrients, various growth factors, and molecular oxygen to meet their heightened metabolic needs, a task, which is fulfilled by angiogenesis [16]. Therapeutic angiogenesis refers to attempts to promote new vessel development, which can be achieved by KRG [17]. Ginsenosides are the major active constituent of ginseng. To date, in excess of 40 different ginsenosides with distinct pharmacological actions have been isolated. Ginsenosides can be categorized into three main categories by their chemical structure, which include the protopanaxadiols (PPD) (e.g. Rb1, Rb2, Rc, Rd, Rg3, Rh2), protopanaxatriols (PPT) (e.g. Re, Rf, Rg1, Rg2, Rh1) and the oleanolic acid derivatives [18]. KRG is rich in ginsenosides and thus exerts a significant pharmacological action on vascular regeneration. In a recent study, Kimura et al. [19] studied mice to examine the effects of total ginseng saponins and various ginsenosides on burn wound healing. The authors showed that ginsenoside Rb1 greatly promoted neovascularization in the sites adjacent to burn wounds at a dose of 100 fg–1 ng per wound area, making it the most effective agent for wound healing. We estimated that, having an angiogenic action, KRG would hasten anastomotic healing. Our results suggest that our hypothesis was true in that they showed impressive angiogenic action in KRG groups, while the control groups continued to have poor capillary circulation. It is well known that oxygen has a critical role in anastomotic healing [20]. However, it is not entirely clear by which cellular and molecular mechanisms of tissue hypoxia impair anastomotic healing. Although hypoxia provides a starting stimulus for neovascularization, its effects are not long-lived. Angiogenesis referring to novel vessel development is critical for wound healing. Vascular endothelial growth factor (VEFG) and nitric oxide (NO) are two critical compounds that operate on a molecular level in the process of angiogenesis [21]. Sengupta et al. [7] showed that ginsenoside Rg1 increased functional neovascularization into a polymer scaffold in vivo, while proliferation and chemo invasion of tube-like capillary formation by human umbilical vein endothelial cells (HUVECs) increased the expression of nitric oxide synthetase, phosphatidylinositol-3 kinase, and the Akt pathway. Similarly, Kimura et al. [19] demonstrated that ginsenoside Rb1 stimulated VEGF production and improved skin wound repair. However, Sengupta et al. used greater Rb1 concentrations than Kimura et al (100 fg, 10 pg and 1 ng per wound or per ml), in vivo or in vitro. One study reported that when infused at low doses (6 or 60 μg day-1), ginsenoside Rb1 upregulated Bcl-xL expression and eliminated ischemic neuronal death, although it failed to do so at high doses (3 or 12mg day-1) [22]. The reason why ginsenoside Rb1 appears to be more pharmacologically active at low doses should be further studied. Our results unequivocally showed new capillary formation in the KRG groups, although its molecular mechanisms and contribution to the healing process are not entirely clear.

Anastomosis failure is characterized by excessive collagen degradation or defective new collagen synthesis. Kiyama et al. [23] reported that when they inhibited collagenase activity, they observed reduced collagenolysis by promoting the storage of collagen at the anastomosis site and wound healing. PMNLs possess granulocyte collagenase activity that is held responsible for excessive collagen breakdown and slowing down anastomotic healing. We showed lower inflammatory cell infiltration scores in the KRG group compared to controls, although the difference did not reach statistical significance. We thus selected the amount of tissue hydroxyproline as a marker of collagen synthesis, and found higher hydroxyproline levels in the groups administered POD 3 KRG although we observed similar hydroxyproline levels in groups treated with POD 7. The bursting pressure is a surrogate marker for the mechanical strength of an anastomosis and has been found to increase in a progressive fashion following the establishment of colonic anastomoses. In a study of Sapidis et al., the administration of synbiotics in conjunction with glutamine resulted in increasing the mechanical strength of the anastomosis, thus increasing the bursting pressure and decreasing or effacing of anastomotic dehiscence and limiting bacterial translocation [24]. We found higher bursting pressures in colonic anastomoses of the KRG groups than the controls.

The most well-known effects of KRG are the vasorelaxing effects. Matsuda et al. [25] used the hydrogen gas clearance method to examine the vasorelaxing effects of KRG in rats and found that the perfusion of liver, spleen, kidney, and gastric mucosa was improved by KRG. KRG has also been reported to exert a dose-dependent protective action on gastric mucosa injured by HCl/ethanol- and indomethacin by increasing blood flow to gastric mucosa and inhibiting lipid peroxidation. Fibroblasts constitute the major cells that produce much of the collagen needed during wound healing. These cells start to migrate and accumulate in the wound area at significant numbers by the second day after surgery [25] and then return to normal numbers. Our study demonstrated greater fibroblast migration into the wound area in the KRG group compared to the POD 7 group. Hence, we suggest that KRG increased colonic blood flow by inducing vasorelaxation and stimulating fibroblast migration into anastomosis site.

To date, no study has determined that any KRG dose has a positive effect on anastomotic healing. The KRG dose used in this study was determined on the basis of previously reported doses effective on angiogenesis [20], which was a lower

dose since higher doses did not show any notable effect on angiogenesis. To our best knowledge, our study is the first in this field of research. It is therefore a complicated task to assess the dose and the mode of administration (single dose or continuous treatment) of the agent based on the results of this study. Whereas it is currently unknown exactly which mechanisms of KRG administration lead to improved anastomotic wound healing, it is plausible that this effect is brought about by an increase in neoangiogenesis, fibroblastic activity, and collagen synthesis.

Conclusion

We are of the opinion that our findings may assist clinicians and researchers to develop potential therapies and approaches to improve colonic anastomotic healing and reduce the morbidity and mortality rates of anastomotic leaks. We therefore urge the researchers to conduct further studies to investigate the potential of KRG for improving anastomotic healing and reducing the rate of colonic anastomosis dehiscence.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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